REMARKS/ARGUMENTS

Applicants acknowledge receipt of the Office Communication dated November 26, 2003, and in the current amendment, have corrected the omission of markings in amended claim 1 showing how it was changed. In the foregoing Listing of Claims, claims 1, 9, 11, 13 and 18 are additionally corrected to include the previous amendments that had been made in the *Request for Continued Examination and Response to Final Office Action Dated August 13, 2002*, but which were inadvertently omitted from claims 1, 9, 11, 13, 18 and 25 in the *Amendment and Response to the Office Action Dated May 5, 2003*. Claim 25 is now canceled, and the Status of the Claims has been updated accordingly. Minor amendments to claims 2, 3 and 8 are also included for the purpose of better claim form or better internal consistency of language.

Applicants re-urge the remarks and arguments presented in the *Amendment and Response to the Office Action Dated May 5, 2003*, except for any statements that are not consistent with the corrected claims, as presented herein. To facilitate examination, the Applicants' remarks and arguments in the *Amendment and Response to Office Action of May 5, 2003* are reproduced hereinbelow, except for omission of a few statements that are now viewed as unnecessary in light of the corrections.

1. In the Office Action dated May 5, 2003, the Examiner (1) objected to some of the claims, (2) rejected certain claims under 35 U.S.C. §102(b) as anticipated by U.S. Patent No. 5,393,739 (Bentz et al.), (3) rejected certain claims under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,177,406 (Wang et al.) in view of EP 433,225 (Cerletti et al. 1991), (4) rejected certain claims under 35 U.S.C. § 103(a) as being unpatentable over Wang et al. in view of the combination of Cerletti 1991 and Stelincki et al. (*Plastic and Reconstructive Surgery*, 1998, Vol. 101, pp. 12-19), (5) rejected certain claims under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,150,328 (Wang et al. 2000) in view of the combination of Cerletti 1991 and U.S. Patent No. 5,616,490 (Sullivan et al.), and (6) rejected certain claims under 35 U.S.C. § 103(a) as being unpatentable over Wang et al. 2001 in view of the combination of Bentz et al. and U.S. Patent No. 4,950,483 (Ksander).

2. Applicants gratefully acknowledge the allowance of claim 26, and the Examiner's indication that claims 6 and 18-23 are allowable but for their dependency from rejected claims. Applicants

respectfully request consideration of the foregoing amendments and the following remarks and arguments, and withdrawal of the remaining rejections.

Status of the Claims

3. Claims 1-4, 6, 8, 9, 11, 13, 16-18, 20 and 22-24 have been amended.
Claim 25 has been canceled.
Claims 1-24 and 26 remain pending.
Claim 26 stands allowed.

Objections to the Claims

4. The Office Action of May 5, 2003 objects to claims 6 and 18-23 as depending from rejected claims, but are said to be otherwise allowable. In response, Applicants have rewritten claims 6 and 18 in independent form, including the limitations of claims 1 and 13, respectively. Claims 19-23 depend from now-allowable claim 18 and are believed to also be in condition for allowance.

5. Claim 24 has been amended to recite "composition" instead of "method," so that dependency is proper.

6. Claim 25 stands provisionally objected to in the Office Action. It is said that claim 25 is a substantial duplication of claim 6. In reply, claim 25 has been canceled.

Rejection of Claims Under 35 U.S.C. § 102(b)

7. Claims 9-12 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Bentz et al. The Examiner notes that Bentz et al. teaches a combination of BMP and TGF-β (col. 5, line 9), and that synthetic or recombinant forms would be free of histones and ribosomes (col. 5, lines 19-20). In reply, Applicants respectfully traverse at least for the reason that a combination of synthetic or recombinant BMP protein and TGF-β protein, while apparently lacking histones and/or ribosomes, would still not necessarily be the same as the composition of any of claims 9 -12.

> To anticipate a claim, a single reference must teach every element of the claim -- either expressly or inherently (MPEP 2131.01). A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a

single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

In claims 9-12, as currently amended, each and every limitation is not taught by the Bentz et al. reference. Claims 9 and 11 require that the mixture of proteins has been treated to deplete histone proteins, and that native post-translation modifications of at least one of the growth factors are retained. The amendments are supported in the Specification at page 19, lines 2-3; 4-5; and 13-16, for example, where it is taught that the functional derivatives of some of the components of the BP "cocktail" are in a glycosylated or phosphorylated form; and that "care must be taken in preparing BP not to degrade these functional modifications." It would not be reasonable to conclude that simply combining one or more purified synthetic or recombinant BMP protein with a TGF-β protein, as in Bentz et al., would result in exactly the same mixture of bone derived morphogenetic proteins, from which histones and/or ribosomes are subsequently depleted so that one or more of the BMPs retain post-translation modifications such as phosphorylation or glycosylation. For at least the foregoing reasons, claims 9-12 are believed to distinguish over the Bentz et al. reference.

Rejection of Claims Under 35 U.S.C. § 103(a)

8. Claims 1, 3-5, 7 and 8 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Wang et al. 2001 in view of Cerletti et al. The Office Action takes the position that recombinant proteins, which are free of histones and ribosomal proteins, are taught at col. 3, lines 27-43 of Wang et al. 2001. It is also said that purification from bovine bone is taught at col. 5, lines 60-67; col. 6; and col. 7, lines 1-4 of the same reference. While it is acknowledged that Wang 2001 does not teach the use of TGF-β to treat skin wounds, it is said that Cerletti et al. teaches the use of TGF-β-like protein to treat burns and incisional wounds (at page 5, lines 13-16 of Cerletti et al.). In the Office Action, it is concluded that it would be obvious to combine the teachings of Wang et al. 2001 and Cerletti et al. because the references teach that BMP-3, TGF-β1, TGF-β2 and TGF-β3 can be used for the same purpose.

Claim 1 has been amended to require a bone-derived mixture of proteins that has "been treated to deplete histones and/or ribosomes." The mixture of proteins used in the method resulting from the combination of Wang et al. 2001 and Cerletti et al. would not have been subjected to treatment(s) to deplete histones and/or ribosomes, as neither reference teaches or suggests such treatments.

Claim 3 has been amended to require that any additional growth factors are in their native post-translation modified form. For better internal consistency of language, claim 3 has also been amended to state "at least one said growth factor." Claim 4 depends from amended claim 1 and further requires that at least one growth factor is at least partially phosphorylated and glycosylated. Neither reference teaches or suggests that either growth factor should be phosphorylated or glycosylated or otherwise retained in a native post-translation modified form when used for promoting wound healing.

Claim 8, as previously presented, includes similar limitations and has been amended only to improve claim form.

Claims 5 and 7 depend from claim 1 and recite specific requirements as to the histones (claim 5) and ribosomes (claim 7) which are absent from the protein mixture. Clearly neither of the cited references teach or suggest a bone-derived protein mixture with these specific limitations.

9. Claim 2 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Wang et al. 2001 in view of Cerletti et al. and further in view of Stelincki et al. The Examiner takes the position that it would be obvious to one of ordinary skill in the art to combine the teachings of Stelincki et al. with those of Wang et al. 2001 and Cerletti et al. to combine the three factors, BMP-2, BMP-3 and TGF-β, to treat wound healing. In reply, Applicants submit that even if one were to combine the teachings of the references, one would still not have the same method as claim 2. Combining the teachings of Wang et al. 2001, Cerletti et al. and Stelincki et al. to provide a method of promoting wound healing that employs a mixture of certain recombinant BMPs and TGF-β2 proteins would not ensure that those recombinant proteins retained their native post-translation modifications (*e.g.*, phosphorylation or glycosylation). Claim 2 has been amended to require at least one bone-derived growth factor, and has been further amended to require that any additional bone-derived growth factor in the composition is in its native post-translation modified form. The combined references do not teach or suggest that a bone-derived mixture of proteins would have been subjected to treatment(s) to deplete histones and/or ribosomes. The combined references also do not teach or suggest ensuring that a growth factor is phosphorylated, glycosylated, or otherwise retains its native post-translation modified form when used for promoting wound healing. For better internal consistency of language, claim 2 has also been amended to state "at least one said growth factor."

10. Claim 24 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Wang et al. 2001 in view of Cerletti et al. and further in view of Sullivan et al. It is said that Sullivan et al. teaches TNF-α as a means of treating inflammatory disease, and that it would be obvious to combine the references as suggested because Sullivan et al. teach that inflammation is an early step in wound healing, involving TNF-α (at col. 1, lines 17-56 of Sullivan et al.). Without concurring with the Office Action's position as to the teaching of Sullivan et al., Applicants submit that even if the references were combined as suggested in the Office Action, one would still not have the same composition containing an inhibitor of IL-1, IL-6 or TNF-α because the combined references would not provide a product mixture that had been treated to remove ribosomal proteins. Moreover, there would be no reasonable expectation that the product of the combined references would include growth factors having any native post-translation modifications.

11. Claims 13-17 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Wang et al. 2000 in view of Bentz et al. and further in view of Ksander et al. It is said that Wang et al. 2000 teaches combinations of BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, TGF-β and FGF for wound healing (col. 2, lines 34-65 of Wang et al. 2000). It is said that Wang et al 2000 teaches recombinant proteins free of other proteins (col. 5, lines 5-8); and natural sources are taught at col. 7, lines 63-67; col. 8; and col. 9, lines 1-7. It is said that it would be obvious to combine FGF-1 as taught by Bentz et al. and the TGF-β1, TGF-β2, TGF-β3 isoforms as taught by Ksander et al. with the BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7 and TFG-β mixture of Wang et al. 2000, to provide the claimed compositions.

Claim 13 has been amended to recite "bone-derived mixture" and "said mixture having been treated to deplete histones and/or ribosomes," and "said growth factors retaining native post-translation modifications." Without agreeing that the references are combinable as suggested in the Office Action, it is submitted that even if the isolated or recombinant growth factors were combined in the suggested manner, the resulting mixture would not necessarily have been treated to deplete histones and/or ribosomes and would not necessarily possess any native post-translation modifications of the growth factors. Claims 14-17 depend from claim 13 and include the same limitations. Claim 17 has been amended to clarify the further addition of a recombinantly produced protein. Claims 13-17, as amended, are believed to be non-obvious over the cited references.

Conclusion

12. Applicants may have at times referred to claim limitations in shorthand fashion, or may have focused on a particular claim element. This discussion should not be interpreted to mean that the other limitations can be ignored or dismissed. The claims must be viewed as a whole, and each limitation of the claims must be considered when determining the patentability of the claims. Moreover, it should be understood that there may be other arguments with respect to patentability which have yet to be raised, but which may be raised in the future. The format of this Amendment and Response to Office Action is believed to conform with the Revised Amendment Practice as described in "Changes To Implement Electronic Maintenance of Official Patent Application Records," 68 Fed. Reg. 38611 (June 30, 2003).

All of the pending claims are believed to be free of the prior art, and reconsideration and withdrawal of the rejections are respectfully requested. If a telephone conference would facilitate the resolution of this matter, the Examiner is invited to telephone the undersigned representative. Should any fees have been inadvertently omitted, or if any additional fees are required or have been overpaid, please appropriately charge or credit those fees to Deposit Account Number 03-2769 of Conley Rose, P.C., Houston, Texas, and consider this a petition for any necessary extension of time.

Respectfully submitted,

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